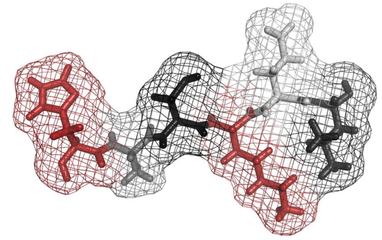
Generalized Protein Scaffold Selection And Diversification Strategies



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Protein Ligand Scaffolds

***Introduction*:**

- Sequence space is massive and rarely contains useful proteins
- Protein scaffolds can function as stable platforms to scan for sequences demonstrating a certain phenotype
- Directed evolution techniques can elucidate binding proteins capable of targeting human biomarkers for cancer and other diseases

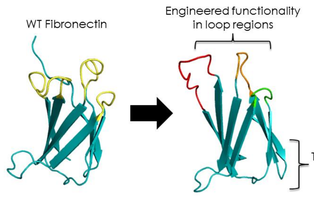
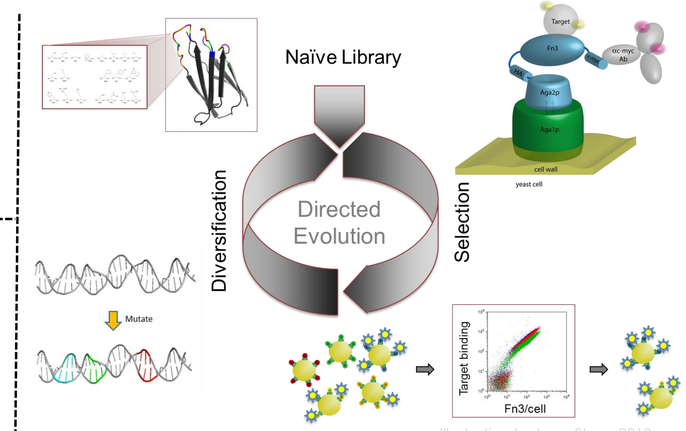


Illustration by Larry Stern, 2013



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***Aim*:**

- Develop an analytical system capable of evaluating scaffold success prior to experimentation
- Accelerate directed evolution by constructing mutational algorithms capable of that targeting functional regions of sequence space

Acknowledgements

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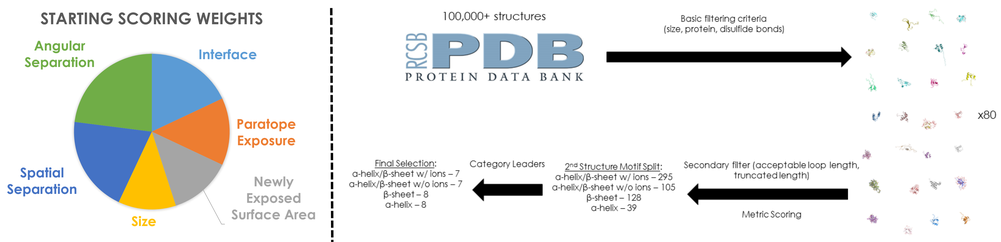
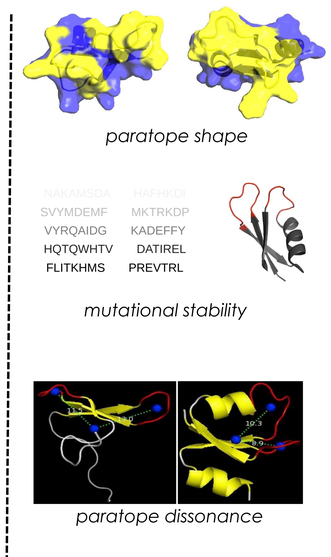
Objective Scaffold Selection

Hypothesis: After determining the prevalence of thirty scaffold candidates after competitive evolution, we can determine numerical weights for the biophysical properties that drive certain scaffold success

Scaffold election basis:

- small size (<65 amino acids)
- paratope type: loop, helix, sheet
- paratope shape
- paratope dissonance
- paratope size
- mutational stability
- no disulfide bonds





Diversification Strategies

Hypothesis: Efficacious partitions of protein sequence space can targeted in combinatorial libraries using scaffold-specific data balancing both stability and functionality

How do we determine which mutations lead to most effective libraries for molecular binding?

Binding Library Sequence Network